The effect of treatment with selective serotonin reuptake inhibitors in comparison to placebo in the progression of dementia: a systematic review and meta-analysis

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Abstract

Background: selective serotonin reuptake inhibitors (SSRIs) may affect the neurodegenerative process of dementia, enhancing cognition. This systematic review aims to determine whether SSRIs influence cognitive performance, mood and function in people with any type of dementia.

Method: randomised placebo-controlled studies of SSRIs in people with dementia, which recorded cognitive outcomes, were identified in ALOIS (ALzheimer’s and cOgnitive Improvement Studies register) in April 2013 and updated in January 2015. Data were extracted on cognition, agitation, mood, activities of daily living (ADLs) and adverse events. End of treatment statistics were calculated.

Results: twelve studies met inclusion criteria (1,174 participants), of which seven studies (710 participants) provided data for meta-analysis on cognition. There was no difference in MMSE score at end of treatment; mean difference (MD) was 0.28 (95% CI −0.83 to 1.39) (six studies, 470 participants). For change in MMSE scores, there was a small improvement; MD was 0.53 (95%CI −0.07 to 1.14) (three studies, 352 participants). The remaining studies showed no improvement in cognition.

There was no statistically significant benefit of SSRIs on mood (four studies, 317 participants); standard mean difference (SMD) −0.10 (95% CI −0.39 to 0.2), agitation (three studies, 189 participants); SMD −0.01 (95% CI −0.86 to 0.83), or ADLs at end of treatment (four studies, 336 participants); SMD −0.15 (95% CI −0.45 to 0.15). There was no difference in mortality between the two groups. Study quality was mixed with concerns over incomplete data.

Conclusion: a small number of relatively low-powered studies showed no benefit or harm from SSRIs in terms of cognition, mood, agitation or ADLs. Large, methodologically robust studies are needed.

Keywords: SSRI, dementia, systematic review, placebo, older people

Background

Selective serotonin reuptake inhibitors (SSRIs) are effective in the treatment of depression [1], and other conditions such as obsessive– compulsive disorder, panic disorder and bulimia [2], but whether they have a role in the treatment of dementia is unclear. SSRIs have been used to manage neuropsychiatric symptoms in dementia—for example, a recent Cochrane review supported the use of certain antidepressants for agitation and psychosis [3]—but they are not used clinically to stabilise or improve cognition.

SSRIs are highly selective for the neurotransmitter 5-hydroxytryptamine (SHT, serotonin) receptor and act by increasing the extracellular levels of serotonin through reuptake inhibition into the presynaptic cell [4]. In Alzheimer’s dementia, there are reduced levels of serotonin and its
precursors such as tryptophan [5]. In theory, SSRIs could increase these, promote neurogenesis [6], encourage migration of new neurones to damaged brain areas [7] and decrease inflammation [8]. All of which in turn could affect neurodegeneration and thus have an impact on cognition.

It is unclear whether SSRIs affect cognition in dementia. A review including preclinical and clinical trials found some evidence to support SSRIs as cognitive enhancers [9]. A randomised control trial of fluoxetine versus placebo in mild cognitive impairment showed some improvement [10], whereas a meta-analysis of SSRIs in patients with Alzheimer's disease and co-morbid depression (six studies, 621 participants) [11] found no effect on cognition or depression.

There is therefore a need for an updated review of the evidence for use of SSRIs in patients not just with Alzheimer’s disease, but all subtypes of dementia, without limiting to those with a diagnosis of depression. The primary purpose of this new review was to assess the effect of SSRI medications compared with placebo on cognitive performance in people with dementia. Secondary outcomes were agitation, mood, the patient’s ability to perform activities of daily living (ADLs) and adverse events.

**Methods**

**Search strategy**

The strategy was registered with Prospero in 2013: CRD42013003539 [12]. ALOIS (Alzheimer’s and Cognitve Improvement Studies register) was used to identify all randomised controlled studies using SSRIs in dementia in English. ALOIS is a specialised open-access register maintained by Cochrane Dementia and Cognitive Improvement Group, derived from regular searches of a variety of major healthcare databases including MEDLINE and EMBASE [13]. The search was performed in April 2013 and then again in January 2015 to identify any new studies.

The search was composed of the following terms: Selective Serotonin Reuptake Inhibitors; SSRI; citalopram; escitalopram; fluoxetine; fluvoxamine; paroxetine and sertraline; combined with dementia (including subtypes). (The full search strategy used is shown in Supplementary data 1, available in *Age and Ageing* online).

**Selection criteria**

Two authors (A.J. and H.J.) independently assessed all titles and abstracts, obtained full texts for potentially relevant studies and applied the following inclusion criteria:

- **Study type:** Published randomised placebo-controlled studies. Ongoing studies, studies not available in English and unpublished studies were excluded.
- **Study group:** Individuals with a diagnosis of any type of dementia according to standard criteria. There was no age restriction and any type and severity of dementia was accepted. Participants with an additional diagnosis of depression were accepted. Studies including participants with mild cognitive impairment and/or delirium without a distinct dementia group were excluded.
- **Study intervention:** Placebo-controlled studies of SSRIs. Studies that referred to other antidepressants or used comparisons with other alternative active treatment were accepted if they included SSRI and placebo.
- **Study outcomes:** Cognitive performance assessed by a validated cognitive test. Only one cognitive test was chosen from each study based on our pre-determined ranking system (Supplementary data 2, available in *Age and Ageing* online) [14]. Any discrepancy or uncertainty regarding the eligibility of a study was discussed with a third author (G.M. or S.S.) until consensus was reached. If more than one publication reported data from the same participants, the publication that provided the most detail on our primary aim was used. Data were included as stated in the published papers; original protocols were not retrieved. Data from eligible studies were extracted by two independent reviewers (A.J. and H.J.) using a paper extraction form. Investigators were contacted for any missing data related to the primary aim. Two authors kindly responded and provided their continuous data on cognitive assessment [15, 16].

For studies with a placebo arm and two active arms, only data from the control arm and the SSRI arm were analysed. Methodological quality of included trials was assessed based on criteria listed in the Cochrane's Reviewers Handbook [17]. Review Manager (RevMan5.1) software was used to calculate summary statistics at the end of intervention and follow-up using a random-effects model [18]. Mean difference (MD) was used if studies used the same scales for outcomes, standard mean difference (SMD) if not [17]. Statistical heterogeneity between studies and subgroups was assessed by $I^2$ statistic and interpreted according to the Cochrane Handbook. For dichotomous data, risk ratios (RRs) were reported.

**Results**

In total, 1,928 study abstracts were assessed and 60 full texts were read (Figure 1). Twelve studies met the inclusion criteria.

**Patient characteristics**

The 12 studies recruited 1,174 participants from nine countries (Table 1). Seven studies recruited from outpatient clinics, three studies [24–26] recruited inpatients and two studies [15, 27] did not report the source of participants. The number of participants in each trial (SSRI and placebo participants only) ranged from 10 to 245, with five studies recruiting <50 participants [15, 19, 22, 23, 25]. Nine studies [19–24, 26–28] reported mean ages ranging from 66.3 [19] to 80.9 years [24]. Eight studies [15, 16, 20–22, 24, 26, 28] restricted entry to only those with Alzheimer’s dementia and three [23, 25, 27] recruited participants with vascular dementia and/or Alzheimer’s. One study only recruited participants with frontotemporal dementia using internationally agreed criteria for
diagnosis [19]. Six [15, 20, 24–27] used DSM-IV/DSM-III (depending on the date of the study) to diagnose dementia and five [16, 21–23, 28] used NINCDS-ADRDA.

**Study characteristics**

All 12 studies randomised participants to SSRI or placebo. Four used sertraline [16, 20–22], three fluoxetine [15, 23, 26], three citalopram [24, 27, 28], one paroxetine [19] and one fluvoxamine [25]. Two studies had three arms: SSRI, placebo and a third treatment group [16, 24]. The data from the third group have not been included in this review. In three studies [19, 25, 26], the primary aim was to assess efficacy of SSRI medications as a treatment for cognitive impairment in dementia. The remaining nine studies had this as a secondary aim.

The duration of treatment ranged from 17 days [24] to 39 weeks [16], mean of 14.3 weeks. Some studies incorporated other phases into the study such as a wash out or open-label phase. In 11 studies, the dose of SSRI was gradually increased; some followed a set weekly regime, others allowed clinicians to adjust doses based on response and tolerability [16, 19–28]. Dose adjustment information was not available for one study [15].

All studies reported duration of treatment and measured outcomes at the end of treatment. For all but one trial [20],

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**Figure 1. Flow diagram of selected studies.**
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Sample Population</th>
<th>Entry number</th>
<th>Dementia type and class</th>
<th>Age, years&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sex (male)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>SSRI used</th>
<th>Additional group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auer et al.</td>
<td>1996</td>
<td>USA</td>
<td>–</td>
<td>17</td>
<td>Fluoxetine</td>
<td>13</td>
<td>Placebo</td>
<td>Fluoxetine</td>
<td>–</td>
</tr>
<tr>
<td>Banerjee et al.</td>
<td>2011</td>
<td>UK</td>
<td>Outpatient</td>
<td>107</td>
<td>Sertraline, NINCDS-ADRDA</td>
<td>–</td>
<td>SSRI 32%</td>
<td>Sertraline</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Deakin et al.</td>
<td>2003</td>
<td>UK</td>
<td>Outpatient</td>
<td>10</td>
<td>Alzheimer's Disease, NINCDS-ADRDA</td>
<td>–</td>
<td>70%</td>
<td>Paroxetine</td>
<td>–</td>
</tr>
<tr>
<td>Weintraub et al.</td>
<td>2010</td>
<td>USA</td>
<td>Outpatient</td>
<td>67</td>
<td>Alzheimer's Disease, DSM IV</td>
<td>SSRI, 76.5 (8)</td>
<td>54%</td>
<td>Sertraline</td>
<td>–</td>
</tr>
<tr>
<td>Finkel et al.</td>
<td>2004</td>
<td>Finland</td>
<td>Outpatient</td>
<td>124</td>
<td>Alzheimer's Disease, NINCDS-ADRDA</td>
<td>Total 76.3 (7.5)</td>
<td>43%</td>
<td>Sertraline</td>
<td>–</td>
</tr>
<tr>
<td>Lyketsos et al.</td>
<td>2003</td>
<td>USA</td>
<td>Outpatient</td>
<td>24</td>
<td>Alzheimer's Disease, NINCDS-ADRDA</td>
<td>Total 77 (8.4)</td>
<td>SSRI 18%</td>
<td>Sertraline</td>
<td>–</td>
</tr>
<tr>
<td>Petracca et al.</td>
<td>2001</td>
<td>Argentina</td>
<td>Outpatient</td>
<td>17</td>
<td>Alzheimer's Disease and Vascular Dementia, NINCDS-ADRDA</td>
<td>SSRI, 70.2 (6.3)</td>
<td>SSRI 53%</td>
<td>Fluoxetine</td>
<td>–</td>
</tr>
<tr>
<td>Pollock et al.</td>
<td>2002</td>
<td>USA</td>
<td>Inpatient</td>
<td>31</td>
<td>Alzheimer's Disease DSM-IV</td>
<td>SSRI, 80.9 (6.9)</td>
<td>SSRI 79%</td>
<td>Citalopram</td>
<td>Perphenazine</td>
</tr>
<tr>
<td>Olafsson et al.</td>
<td>1992</td>
<td>Denmark</td>
<td>Inpatient</td>
<td>22</td>
<td>Alzheimer's Disease Vascular Dementia, DSM-III</td>
<td>SSRi 81&lt;sup&gt;c&lt;/sup&gt;</td>
<td>SSRI 36%</td>
<td>Fluvoxamine</td>
<td>–</td>
</tr>
<tr>
<td>Mowla et al.</td>
<td>2007</td>
<td>Iran</td>
<td>Inpatient</td>
<td>41</td>
<td>Alzheimer's Disease DSM IV</td>
<td>Total 69.2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>46.5%</td>
<td>Fluoxetine</td>
<td>–</td>
</tr>
<tr>
<td>Nyh et al.</td>
<td>1990</td>
<td>Sweden, Norway and Denmark</td>
<td>–</td>
<td>44</td>
<td>Alzheimer's Disease and vascular dementia, DSM-III</td>
<td>Total 77.6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>22%</td>
<td>Citalopram</td>
<td>–</td>
</tr>
<tr>
<td>Porsteinsson et al.</td>
<td>2014</td>
<td>USA/Canada</td>
<td>Outpatient</td>
<td>94</td>
<td>Alzheimer's Disease NINCDS-ADRDA</td>
<td>Total 78 (8)</td>
<td>15%</td>
<td>Citalopram</td>
<td>–</td>
</tr>
</tbody>
</table>

FTD, frontotemporal dementia; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition; DSM IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria.

<sup>a</sup>Mean (standard deviation) unless stated otherwise.

<sup>b</sup>Overall % unless otherwise stated.

<sup>c</sup>Median.

<sup>d</sup>No standard deviation given.
the end of treatment was the termination point of the trial with no subsequent follow-up reported.

Cognition

Mean score after treatment: there was no difference in mean MMSE (Mini Mental State Examination) scores at the end of treatment between SSRI and placebo groups. Trials that used MMSE scoring lasted between 6 [23] and 39 weeks [16], mean of 16.75 weeks. Eight studies (841 participants) [15, 16, 20-23, 26, 28] used MMSE to assess cognition before and end of treatment, with six (470 participants) [15, 16, 22, 23, 26, 28] reporting the mean MMSE at end of treatment, allowing data to be combined in meta-analysis. The MD at the end of treatment was 0.28 MMSE points (95% CI -0.83 to 1.39) with moderate heterogeneity ($I^2 = 38\%$, $P = 0.15$) (Table 2, Figure 2a). All of these studies except one small study [23] included solely patients with Alzheimer’s disease.

Change in score after treatment: in studies that reported cognitive change, there was less cognitive decline when treated with SSRI. Three of the eight studies (352 participants) [15, 21, 26], all in patients with Alzheimer’s disease, reported the difference in MMSE scores following treatment; MD was 0.53 (95% CI -0.07 to 1.04), $I^2 = 0\%$ $P = 0.92$, Figure 2b). It was not possible to include all studies in the change of score analysis due to lack of availability of primary data.

One study [20] only presented median scores, and so the data could not be incorporated into either meta-analysis, but found no difference between groups. The median score (1st, 3rd quartiles) at the end of treatment was 21 (16.5, 24) and 20 (14.75, 24) in the control. Treatment effect was $\chi^2 = 0.5$ (degrees of freedom 1); $P = 0.50$.

Four studies (196 participants) [19, 24, 25, 27] including patients with Alzheimer’s vascular or frontotemporal dementia showed no difference in cognition at the end of treatment with SSRI. One (10 participants) [19] found no significant differences on the Neuropsychiatric Inventory between paroxetine and placebo. For one study in patients with Alzheimer’s disease [24], the Neurobehavioural Factor cognition score from baseline to study termination was -0.22 for citalopram and 0.06 for placebo (readings taken from graph). Within the citalopram group, this was a statistically significant improvement from baseline; however, the difference in the change of score between the citalopram and placebo group was not statistically significant. Two studies [25, 27] in patients with Alzheimer’s or vascular dementia found no difference in cognitive subscale scores on the GBS (Gottfries–Bråne–Steen) rating scale. At the end of treatment, the median (range) was 38 (10-62) in the SSRI group and 42 (12-60) with placebo in one study [25], and in the other [27] there was no difference between the groups ($T = 32 (51), P = 0.321$) (Table 2).

The quality of the studies, as reported, was mixed, and the results should be interpreted with caution. For many studies, the proportion of incomplete outcome data was a concern and at risk of introducing bias. Across the 12 studies, 338 of 1,174 participants (29%) withdrew prior to the final assessment. At least 157 of these were from the SSRI group; one study [22] did not differentiate the groups

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Table 2. Results of studies included in systematic review of SSRIs and placebo in the progression of dementia (ordered by reference number)

<table>
<thead>
<tr>
<th>Author</th>
<th>Highest ranking cognition test</th>
<th>SSRI cognition score</th>
<th>Placebo cognition score</th>
<th>Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>End of treatment</td>
<td>Baseline</td>
</tr>
<tr>
<td>Auer et al. [15]</td>
<td>MMSE</td>
<td>12.94 (8.03)</td>
<td>11.77 (7.66)</td>
<td>32.4 (7.2)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Banerjee et al. [16]</td>
<td>MMSE</td>
<td>18.5 (6.7)</td>
<td>17.4 (7.64)</td>
<td>18.2 (7.4)</td>
</tr>
<tr>
<td>Deakin et al. [19]</td>
<td>Neuropsychiatry, Inventory</td>
<td>–</td>
<td>32.4 (7.2)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Weintraub et al. [20]</td>
<td>MMSE</td>
<td>21 (17, 35)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>21 (16.5, 24)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>19.5 (15, 23.5)&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Finkel et al. [21]</td>
<td>MMSE</td>
<td>18.8 (0.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0 (0.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18.0 (0.5)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lyketsos et al. [22]</td>
<td>MMSE</td>
<td>17.5 (6.5)</td>
<td>16.1 (8.5)</td>
<td>16.3 (6.8)</td>
</tr>
<tr>
<td>Petracca et al. [23]</td>
<td>MMSE</td>
<td>23.2 (4.5)</td>
<td>23.1 (6.8)</td>
<td>23.2 (5.3)</td>
</tr>
<tr>
<td>Pollock et al. [24]</td>
<td>Neurobehavioral subscale</td>
<td>–</td>
<td>0.22&lt;sup&gt;e&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Ofstead et al. [25]</td>
<td>GBS subscale</td>
<td>43 (3-62)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>38 (10-62)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>40 (15-62)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mortha et al. [26]</td>
<td>MMSE</td>
<td>18.6 (7.3)</td>
<td>17.2 (6.6)</td>
<td>16.3 (4.1)</td>
</tr>
<tr>
<td>Nyth et al. [27]</td>
<td>MMSE</td>
<td>38.2 (2.5)</td>
<td>13.6 (2.1)</td>
<td>20.1</td>
</tr>
<tr>
<td>Porsteinson [28]</td>
<td>MMSE</td>
<td>17.0 (6.2)</td>
<td>16.83 (2.95)</td>
<td>14.4 (6.9)</td>
</tr>
</tbody>
</table>

Data are mean cognition score (standard deviation) unless otherwise stated.

MMSE, Mini Mental State Examination; GBS, Gottfries–Bråne–Steen geriatric rating scale; ADL, activities of daily living; AE, adverse events.

<sup>a</sup>Supplementary data 2, available in Age and Aging online.

<sup>b</sup>SE (standard error).

<sup>c</sup>Median.

<sup>d</sup>1st and 3rd quartiles.

<sup>e</sup>Mean change in score from baseline (end treatment value not available).

<sup>f</sup>Range.
from which the six participants withdrew. Six studies [16, 21, 23, 25–27] had a significant drop out rate (>5% [10]) and did not use intention-to-treat analysis. There was no statistically significant difference between the two groups in terms of premature trial withdrawal (T-value = 0.44 and \( P = 0.66 \)). The main reasons for withdrawal were loss of efficacy, administrative reasons and adverse effects. Several studies also lacked sufficient information to determine risk of bias in relation to randomisation, allocation and blinding methods. The risk of bias for each trial is detailed in Supplementary data, Table 1, available in Age and Ageing online.

**Mood**

There was no difference in mood at the end of treatment between the SSRI and placebo group. Four studies (317 participants) [16, 22, 23, 26] reported depression scores and demonstrated an SMD of \(-0.10\) (95% CI, \(-0.39 to 0.2\), \( I^2 = 37\% P = 0.19 \); Supplementary data, Figure 1, available in Age and Ageing online). The remaining eight studies either did not examine mood or did not report the results in a format compatible with the meta-analysis.

**Agitation**

There was no difference in mean agitation scores at the end of treatment. Three studies [19, 24, 28] reported agitation, of which two [19, 28] could be included in meta-analysis (189 participants); (SMD = \(-0.01\) 95% CI \(-0.86 to 0.83\), \( I^2 = 70\% P = 0.07 \); Supplementary data, Figure 2, available in Age and Ageing online). The remaining trial [24] showed a significantly greater improvement in agitation/aggression (from baseline using the Neurobehavioural Factor Score) in the SSRI group (0.98) compared with placebo (0.38) (readings taken off graph; Kruskal–Wallis test \( \chi^2 = 6.7, \text{df} = 2, P < 0.04 \)). While this result is promising, methods used for concealment of allocation and randomisation were unclear, raising the possibility of selection bias. Nine studies did not examine agitation as an outcome.

**Patient’s ability to perform activities of daily living**

There was no difference in a patient’s ability to complete ADLs between the two groups. Four studies (336 participants) [22, 23, 26, 28] reported participants’ ability to perform ADLs at the end of treatment (SMD = \(-0.15\), 95% CI \(-0.45 to 0.15\), \( I^2 = 41\% P = 0.17 \); Supplementary data, Figure 3, available in Age and Ageing online).

**Adverse events and mortality**

There was no increase in mortality with SSRI compared with placebo. Four studies [16, 20, 27, 28] (624 participants) reported a total of 13 deaths. The risk ratio (RR) for death in the SSRI group was 0.91 (95% CI \(0.33 to 2.50\)). Adverse events were reported in all but two studies [15, 19] and were collected either systematically or volunteered by the patient. RR for the number of participants experiencing at least one adverse event was 1.25 (95% CI 0.67 to 2.31, \( I^2 = 87\% P < 0.001 \) favouring placebo [16, 20, 27, 28]. In studies reporting the number of adverse events rather than the number of patients experiencing an event [21, 23], there were 143 adverse events with sertraline, 119 with placebo. One study [24] found no significant change in total UK Side

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSRI</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Auer 1996</td>
<td>11.77</td>
<td>7.66</td>
<td>17</td>
<td>11.85</td>
<td>9.03</td>
<td>13</td>
<td>3.1%</td>
</tr>
<tr>
<td>Lyketsos 2003</td>
<td>16.1</td>
<td>8.5</td>
<td>24</td>
<td>16.8</td>
<td>7.1</td>
<td>20</td>
<td>5.2%</td>
</tr>
<tr>
<td>Petracca 2001</td>
<td>23.2</td>
<td>6.8</td>
<td>17</td>
<td>23.9</td>
<td>5.9</td>
<td>24</td>
<td>6.7%</td>
</tr>
<tr>
<td>Banerjee 2011</td>
<td>17.4</td>
<td>7.64</td>
<td>53</td>
<td>16.63</td>
<td>7.12</td>
<td>56</td>
<td>12.3%</td>
</tr>
<tr>
<td>Mowla 2007</td>
<td>17.2</td>
<td>6.63</td>
<td>41</td>
<td>17.4</td>
<td>3.7</td>
<td>41</td>
<td>33.6%</td>
</tr>
<tr>
<td>Porsteinsson 2014</td>
<td>16.83</td>
<td>2.9503</td>
<td>85</td>
<td>15.33</td>
<td>2.9331</td>
<td>79</td>
<td>39.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.20; Chi² = 8.10, df = 5 (\( P = 0.15 \)); \( \text{I}^2 = 38\% \)
Test for overall effect: \( Z = 0.49 (P = 0.62) \)

**Figure 2.** (a) Mean MMSE scores at end of treatment (ordered by weighting). (b) Mean difference between MMSE scores before and after treatment (ordered by weighting).
Effect Rating Scale score in any of the groups ($F = 1.49$, df = 2, 81, $P = 0.23$). Three studies [22, 25, 26] reported the most common side effects in both groups. Side effects were gastrointestinal, neurological and autonomic disturbances.

Discussion

Summary of key findings

Twelve completed studies comparing SSRIs with placebo were identified, of which seven provided data that could be used in a meta-analysis on cognition [15, 16, 21–23, 26, 28]. Sertraline was the most commonly used SSRI. All participants had a formal diagnosis of dementia, mostly Alzheimer's disease or vascular dementia, but none of the studies stipulated how long this had to have been present. Some, but not all, studies required participants to have depression at the point of entry. The duration of treatment varied from days to months with a mean of 14.3 weeks. Only one study [19] followed up participants after treatment.

Overall, there were no beneficial effects of SSRIs on cognition, with the meta-analysis of MMSE scores at end of treatment demonstrating no statistically significant difference between SSRI and placebo. There was no statistical benefit of SSRI on mood, agitation or ADLs, though the number of studies is small and there was methodological bias in these studies. SSRIs may not be effective in treating depression in patients with dementia [11, 16]. Number of deaths was low with no difference between the groups. There was no statistically significant difference in side effects between the two groups.

Limitations of included studies

It is possible that variations in the quality of the evidence may have influenced the results of this review. The studies were generally small, the largest recruiting 245 participants [21], and were of mixed quality, with many displaying multiple different sources of bias. Some lacked important methodological detail, for example on sequence generation and allocation concealment, making it difficult to determine the risk of bias. The funding source was declared in the majority of the trials, with occasional links to the pharmaceutical industry (e.g. funding [21], provision of drugs [16]).

All participants were generally recruited from tertiary centres, which often have more complex patients with more challenging symptoms. It is therefore unclear whether the findings can be extrapolated to the overall dementia population. The severity of dementia of participants included in the meta-analysis also varied, with mean scores ranging from 11 to 24 in the meta-analysis. It is therefore also feasible that there may be differences in effect depending on the stage of disease. Most studies did not exclude participants who also had concurrent depression and this could have acted as a confounding factor in influencing any changes to a patient’s cognition [29]. Cognition scores may have also been affected for other reasons, including hearing impairment or non-English speaking participants.

The lack of long-term treatment and follow-up after treatment is a major limitation. From studies in participants with depression, it is known that SSRIs take time to show benefit and the dosage required can vary [2]. Some studies only lasted 6 weeks and had strict titration schedules. If cognitive tests are repeated, there is the likelihood of practice effects, and this may mask a decline in cognition, though the effects would be similar in both groups. It is unlikely that cognitive change in a general, 30-point, cognitive test like the MMSE would be detectable over a period of several weeks. Although there was no significant difference in the withdrawal rate between the SSRI and placebo groups, there was an overall high premature drop out of 29% with lack of efficacy and side effects being the main reasons. Ten studies reported side effects, but not all explained how these were collected.

Limitations of the review

The search criteria were deliberately broad to reduce the likelihood of any relevant published studies being missed when searching ALOIS. The main weakness of the search strategy was that any grey literature or unpublished studies would have been missed. Reported data were not checked against original published protocols and so this review is reliant on the reporting of the primary investigators.

The majority of studies ($n = 8$) included only patients with Alzheimer's disease (DSM-III, DSM-IV, or NINCDS-ADRDA criteria) [15, 16, 20–22, 24, 26, 28]. Three included patients with either Alzheimer's or vascular dementia [23, 25, 27], and one just patients with frontotemporal dementia [19]. The majority of patients in the meta-analysis had Alzheimer's disease. Data were insufficient to establish whether dementia subtype affected response to SSRI.

Conclusion

A small number of relatively low-powered studies show no benefit or harm from SSRIs in terms of cognitive outcomes in people with dementia. There is insufficient data to say whether SSRIs are beneficial for cognition, and there is some suggestion of increased side effects. Future studies require adequate numbers of different dementia subtypes to allow subgroup analyses, a longer duration of follow-up, systematic reporting of adverse events and clearer reporting of factors that may bias the results.

Key points

- In patients with dementia, there was no evidence of benefit or harm from SSRIs in terms of cognition, mood, agitation or ADLs.
- SSRIs were generally well tolerated with no increase in mortality, but premature withdrawal from studies was high.
- Large, methodologically robust studies are required.
Supplementary data

Supplementary data mentioned in the text are available to subscribers in Age and Ageing online.

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Conflicts of interest

None declared

References


Effect of treatment with SSRIs in dementia

Ambulatory blood pressure monitoring in older people with dementia: a systematic review of tolerability

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Abstract

Background: ambulatory blood pressure monitoring (ABPM) may be helpful for the management of hypertension, but little is known about its tolerability in people with dementia.

Objective: to review the published evidence to determine the tolerability of ABPM in people with dementia.

Methods: English language search conducted in MEDLINE and EMBASE, using ‘Ambulatory blood pressure’ AND ‘Dementia’ (and associated synonyms) from 1996 to March 2015. Inclusion criteria: people diagnosed with dementia AND in whom blood pressure was measured using ABPM. The initial search was undertaken using title and abstract reviews, with selected papers being agreed for inclusion by two reviewers. Potentially eligible papers were assessed, and high-quality papers were retained. Two reviewers agreed the abstracted data for analysis. Meta-analysis was used to combine results across studies.

Results: of the 221 screened abstracts, 13 studies (6%) met inclusion criteria, 5 had sufficient data and were of sufficient quality, involving 461 participants, most of whom had mild–moderate dementia. 77.7% (95% CI 62.2–93.2%) were able to tolerate ABPM; agreement with office BP was moderate to weak (two studies only—coefficients 0.3–0.38 for systolic blood pressure and 0.11–0.32 for diastolic blood pressure). One study compared home BP monitoring by a relative or ambulatory BP monitoring with office BP measures and found high agreement (κ 0.81). The little available evidence suggested increased levels of dementia being associated with reduced tolerability.

Conclusions: ABPM is well tolerated in people with mild–moderate dementia and provides some additional information over and above office BP alone. However, few studies have addressed ABPM in people with more severe dementia.

Keywords: hypertension, dementia, ambulatory blood pressure monitoring, older people